Remarks

Claims 1-9, 12-23 and 27-30 are pending in the subject application. Applicants acknowledge that claims 20-23, 27 and 28 have been withdrawn from further consideration as being drawn to a non-elected invention. By way of this amendment, claims 20-23 and 27-28 have been canceled and new claims 31-33 have been added. Support for the newly presented claims can be found, for example, in previously pending claim 1 and pages 12-15 of the as-filed application. Accordingly, claims 1-9, 12-19 and 29-33 are currently before the Examiner and claims 1-9, 12-19 and 29-33 read on the elected invention. Favorable consideration of the pending claims is respectfully requested.

Prior to the issuance of another Office Action in this matter, Applicants request the courtesy of an interview to discuss the rejections of record and the previously and newly presented claims.

Claims 1-9 and 12-19 remain rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that the specification is enabled for method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-881)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, but is not enabled for method for producing any other heterodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein any and all domains of the TCR-complex has been modified by mutagenesis to obtain the sterically arranged groups on TCR chains. Applicants respectfully assert that the claims are enabled and traverse the rejection of record.

The Office Action argues that the previously submitted arguments were not found persuasive for the following reasons (see the paragraph bridging pages 3-4 of the Office Action dated March 6, 2009):

> The scope of the instant claims encompasses method for producing any hetrodimeric specific wild-type or chimeric TCR with any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-complex has been modified by mutagenesis and the functionality and stability of the TCR is maintained. Although it was known how to make mutated TCRs, how to introduce them into cells and how to test TCR functionality, the state of the art at the time of filing was such that the TCR is the most intricate membrane receptor structures known in the art, wherein any mutation

> in the TCR-complex would cause unintentional conformational changes rendering the scope of invention as claimed highly unpredictable. It was unpredictable at the time of the invention whether the mutations, including reciprocal exchange, introduced to various TCR domains, including extracellular domain, variable domain, constant domain, connecting peptides, transmembrane domain and intracellular domain, would be able to maintain TCR functionality and stability. In instant case producing wild-type or chimeric TCR receptors specific to a particular antigen and to maintain its functionality and stability, wherein the first and second chain mutated to provide sterically arranged sites is not considered routine in the art and without sufficient guidance to a specific TCR structure associated with corresponding mutated sites designated on each TCR chain, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner must provide evidence or technical reasoning substantiating those doubts. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); and MPEP Section 2164.04.

With respect to these reasons for maintaining the rejection of record, Applicants note that the scope of the claims does not encompass the modification of "any and all domains (*i.e.*, extracellular, transmembrane and intracellular domains) of the TCR-complex" by mutagenesis such that "the functionality and stability of the TCR is maintained". Rather, the claims indicate that a "surface" on a first and second chain are mutagenized in a manner that allows for the introduction of sterically projecting and sterically recessed groups into each respective polypeptide chain (see claim 1, lines 6-9 and 14-27) **such that TCR functionality and stability is not impaired**. As noted in the as-filed specification (at pages 6-7), a "surface" is the area of a TCR that interacts with a particular area of the second chain of the TCR. Applicants further note that the crystal structure of the T cell receptor had been resolved at the 2.5 Angstrom level and that the various "surfaces" that interact with one another were known at the time the instant application was filed (see Garcia *et al.*, *Science*, 1996, 274:209-219, for example, pages 213-214, "The Cα-Cβ interface" and "Elbow region", a copy of which was attached to the previous for the convenience of the Examiner). In the Advisory Action issued in this matter, the Office Action argues that TCRs having different amino acid sequences would have different "surfaces" that interact. Applicants note that Garcia *et al.* and the as-filed specification (page 3, paragraph 1) discuss the constant regions of the TCR alpha and beta chains,

that the constant regions of these polypeptides have a relatively high degree of sequence identity between different alpha and beta chains, and that no evidence has been produced by the Patent Office demonstrating that various surfaces within the TCR and/or the constant regions of that alpha and beta chains of the TCR show a high degree of sequence variability. Thus, it is respectfully submitted that the Patent Office has failed to establish that basis for maintaining the rejection of the claims in this matter, particularly for claim 14 and 30.

Applicant also notes that the Office Action argues that the claims fall "in the realm of gene therapy" and that the state of the art, with respect to gene therapy *in vivo*, was unpredictable. The Office Action argues that the greatest challenge in this area was the efficient transfer and stable expression of a transgene in a target tissue and that the rejection of record was maintained as the claims fail to recite specific condensing agents and/or targeting agents. In this regard, Applicants, again, note that methods of delivering nucleic acids to target cells were known to those skilled in the art at the time the invention was made and that particular targeting agents and/or condensing agents need not be recited in the claims to satisfy the enablement requirements of section 112. However, it is noted that claim 5 indicates that nucleic acids are delivered, *in vitro* or *in vivo*, via liposome transfer. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

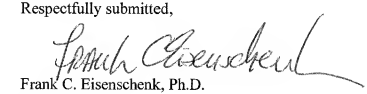
Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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